Gene name: O1-180

cDNA sequence: 1276 bp

"AAGGCGGGGGGGGGGGGGCGCGCGACCCATGTTCCCGGCGAG CACGTTCCACCCCTGCCCGCATCCTTATCCGCAGGCCACCAAAGCCGGGGATG GCTGGAGGTTCGGAGCCAGGGGCTGCCGACCCGCGCCCCCCCTCCTTCCCCC GGCTACAGACAGCTCATGGCCGCGGAGTACGTCGACAGCCACCAGCGGCAC CGCTGCGGTGCAGGTGAACCCGCGCGCGCGACGCCTCGGTGCAGTGTTCACTC CGGGTTCCTGTCAACCCCGTGGCCACGCCGGCGCGCGGGAGATCCCCGCGATC CTGGCAGACCGTAGCCCCGTTCTCGTCCGTGACCTTCTGTGGCCTCCTCCTC ACTGGAGGTTGCGGGAGGCAGCAGACACCCACGAAGGGAGAGGGGAGCCC GGCATCCTCGGGGACCCGGGAACCGGAGCCGAGAGAGGTGGCCGCGAGGAA AGCGGTCCCCCAGCCGCAAGCGAGGAGGGCGATGTTCAGGCTGCAGGGCA GGCCGGGTGGGAGCAGCAGCCACCACCGGAGGACCGGAACAGTGTGGCGGC GATGCAGTCTGAGCCTGGGAGCGAGGAGCCATGTCCTGCCGCAGAGATGGCT CAGGACCCCGGTGATTCGGATGCCCCTCGAGACCAGGCCTCCCCGCAAAGCAC GGAGCAGGACAAGGAGCGCCTGCGTTTCCAGTTCTTAGAGCAGAAGTACGGCT GTGCAGGGCACCAGTAAGGTGTTACTTCAAACAGTTCTGCCGAGTGTGTGAGAA ATCCTACAACCCTTACAGAGTGGAGGACATCACCTGTCAAAGTTGTAAAAGAAC TAGATGTGCCTGCCCAGTCAGATTTCGCCACGTGGACCCTAAACGCCCCCATC GGCAAGACTTGTGTGGGAGATGCAAGGACAAACGCCTGTCCTGCGACAGCAC CTTCAGCTTCAAATACATCATTTAGTGAGAGTCGAAAACGTTTCTGCTAGATGG GGCTAATGGAATGGACAAGTGAGCTTTCTCCCCTCTTCACCTCTTCCCCAA ATTCTTCATGACAGACAGTGTTACTTGGATATAAAGCCTGTGAATAAAAGGTAT TGCAAACAAAAAAAAAAAAAAAAA

Amino Acid sequence: 361aa

"MFPASTFHPCPHPYPQATKAGDGWRFGARGCRPAPPSFLPGYRQLMAAEYVDS HQRAQLMALLSRMGPRSVSSRDAAVQVNPRRDASVQCSLGRRTLQPAGCRASPDA RSGSCQPRGHAGAGRSPRSWQTVAPFSSVTFCGLSSSLEVAGGRQTPTKGEGSPA SSGTREPEPREVAARKAVPQPRSEEGDVQAAGQAGWEQQPPPEDRNSVAAMQSEP GSEEPCPAAEMAQDPGDSDAPRDQASPQSTEQDKERLRFQFLEQKYGYYHCKDCK IRWESAYVWCVQGTSKVYFKQFCRVCEKSYNPYRVEDITCQSCKRTRCACPVRFR HVDPKRPHRQDLCGRCKDKRLSCDSTFSFKYII"

O1-184 cDNA sequence: 1817bp

GTCACAGCTTTCCCCTGCCCGAATATGGTGATCTGTCTCCATTGTCCAGATCA CAGAACCTGGCAATTCAGAGTCTACTGAGGGATGAGGCCTTGGCCATTTCTG CTCTCACGGACCTGCCCCAGAGTCTGTTCCCAGTAATTTTTGAGGAGGCCTTC ACTGATGGATATATAGGGATCTTGAAGGCCATGATACCTGTGTGGCCCTTCCC ATACCTTTCTTTAGGAAAGCAGATAAATAATTGCAACCTGGAGACTTTGAAG GCTATGCTTGAGGGACTAGATATACTGCTTGCACAAAAGGTTCAAACCAGTA GGTGCAAACTCAGAGTAATTAATTGGAGAGAAGATGACTTGAAGATATGGGC TGGATCCCATGAAGGTGAAGGCTTACCAGATTTCAGGACAGAGAAGCAGCCA ATTGAGAACAGTGCTGGCTGTGAGGTGAAGAAAGAATTGAAGGTGACGACT GAAGTCCTTCGCATGAAGGGCAGACTTGATGAATCTACCACATACTTGTTGC AGTGGGCCCAGCAGAAAAAGATTCTATTCATCTATTCTGTAGAAAGCTACT AATTGAAGGCTTAACCAAAGCCTCAGTGATAGAAATCTTCAAAAACTGTACAC GCAGACTGTATACAGGAGCTTATCCTAAGATGTATCTGCATAGAAGAGTTGG CTTTTCTTAATCCCTACCTGAAACTGATGAAAAGTCTTTTCACACTCACACTA GATCACATCATAGGTACCTTCAGTTTGGGTGATTCTGAAAAGCTTGATGAGG AGACAATATTCAGCTTGATTTCTCAACTTCCCACACTCCACTGTCTCCAGAAA CTCTATGTAAATGATGTCCCTTTTATAAAAGGCAACCTGAAAGAATACCTCAG GTGCCTGAAAAAGCCCTTGGAGACACTTTGCATCAGTAACTGTGACCTCTCAC AGTCAGACTTGGATTGCCTGCCCTATTGCCTGAATATTTGTGAACTCAAACAT CTGCATATTAGTGATATATTTATGTGATTTACTCCTTGAGCCTCTTGGTTTT CTCCTTGAGAGAGTTGGAGATACCCTGAAAACCCTGGAATTGGATTCATGTT GTATAGTGGACTTTCAGTTCAGTGCCTTGCTGCCCTAAGCCAATGTTCT CACCTCAGAGAGGTCACTTTCTATGATAATGATGTTTCTCTGCCTTTCTTGAA AACAACTTCTACACCACACAGCCCTGCTGAGTCAGCTGATCTATGAGTGTTAC CCTGCCCCTCTAGAGTGCTATGATGACAGTGGTGTAATACTAACACACAGATT AGAAAGTTTTTGTCCTGAGCTTCTGGATATACTGAGAGCCAAAAGACAGCTC CATAGTGTCTCCTTTCAAACAACCAAATGCTCTAAATGTGGTGGTGCTACAT TTATGATCGGCATACCCAATGTTGCCGTTTTTGTGGAACTACTATAAGCTTGAT TGTGAAACTGAGAAATAGAAACTTAGTATTGGGGGACTGATGAAATCCTAAGT GAATGTCCACTGCTAAATGGAGCATGAAAATGTCAATCACCTAAAAGTCTGA GATACACAGGAAAGTCAATAACTTCCTCTGAGCTGGTGAATGGATGTTGCAT CTGTAGAAAGTATCAAGCACTTGTAGTTTGAATGTGTTACAATAGAAGCACC ATTTTATGAGACTGGCCCAATCTGTTGACTGCATACAATAAATCTGTTGACTT ATTAAATTTTTAAAAAAAAAAAAAAAAAAAAAA

O1-184 amino acid sequence: 426 amino acids

MVICLHCPDQDDSLEEVTEECYSPPTLQNLAIQSLLRDEALAISALTDLPQSLFP VIFEEAFTDGYIGILKAMIPVWPFPYLSLGKQINNCNLETLKAMLEGLDILLAQKV QTSRCKLRVINWREDDLKIWAGSHEGEGLPDFRTEKQPIENSAGCEVKKELKV TTEVLRMKGRLDESTTYLLQWAQQRKDSIHLFCRKLLIEGLTKASVIEIFKTVHA DCIQELILRCICIEELAFLNPYLKLMKSLFTLTLDHIIGTFSLGDSEKLDEETIFSLIS QLPTLHCLQKLYVNDVPFIKGNLKEYLRCLKKPLETLCISNCDLSQSDLDCLPYC LNICELKHLHISDIYLCDLLLEPLGFLLERVGDTLKTLELDSCCIVDFQFSALLPAL SQCSHLREVTFYDNDVSLPFLKTTSTPHSPAESADL

the training of the training training the training traini The state of the s - E Gene name: O1-236

cDNA sequence: 1019bp

"GCCATATTGAGGACCTGCAGTAGAGGTGGAACCCATGACTGGCAGCGCAAAC ACAGTGATAACAGCTGAGCTCCAAGCAAGGACCCAGGACCTTGCCTCACCACA GACATAATCTTTCCCCACAACACCTCCACCAAGCCGCCCTGTAAATCGACATGA GTCGCCACAGCACCAGCAGCGTGACCGAAACCACAGCAAAAAACATGCTCTGG GGTAGTGAACTCAATCAGGAAAAGCAGACTTGCACCTTTAGAGGCCAAGGCGA GAAGAAGGACAGCTGTAAACTCTTGCTCAGCACGATCTGCCTGGGGGAGAAAG CCAAAGAGGAGGTGAACCGTGTGGAAGTCCTCTCCCAGGAAGGCAGAAAACC ACCAATCACTATTGCTACGCTGAAGGCATCAGTCCTGCCCATGGTCACTGTGTC AGGTATAGAGCTTTCTCCTCCAGTAACTTTTCGGCTCAGGACTGGCTCAGGACC TGTGTTCCTCAGTGGCCTGGAATGTTATGAGACTTCGGACCTGACCTGGGAAG ATGACGAGGAAGAGGAAGAGGAAGAGAGAAGATGAAGATGAGGATG CAGATATATCGCTAGAGGAGATACCTGTCAAACAAGTCAAAAGGGTGGCTCCC CAGAAGCAGATGACCATAGCAAAGAAAAAGAAGGTGGAAAAAAGAAGAGGATG AAACAGTAGTGAGGCCCAGCCCTCAGGACAAGAGTCCCTGGAAGAAGAAGAA ATCTACACCCAGAGCAAAGAAGCCAGTGACCAAGAAATGACCTCATCTTAGCAT CTTCTGCGTCCAAGGCAGGATGTCCAGCAGCTGTGTTTTGGTGCAGGTGTCCA GCCCCACCACCCTAGTCTGAATGTAATAAGGTGGTGTGGCTGTAACCCTGTAAC CCAGCCCTCCAGTTTCCGGAGGTTTTTTGGTGAAGAGCCCCCAGCAAGTTCGCC ΑΑΑΑΑΑΑΑΑΑΑΑΑ"

Amino Acid sequence: 207aa

"MSRHSTSSVTETTAKNMLWGSELNQEKQTCTFRGQGEKKDSCKLLLSTICLGEK AKEEVNRVEVLSQEGRKPPITIATLKASVLPMVTVSGIELSPPVTFRLRTGSGPVFLSGLECYETSDLTWEDDEEEEEEEEDEDEDADISLEEIPVKQVKRVAPQKQMSIAKKKVEKEEDETVVRPSPQDKSPWKKEKSTPRAKKPVTKK"

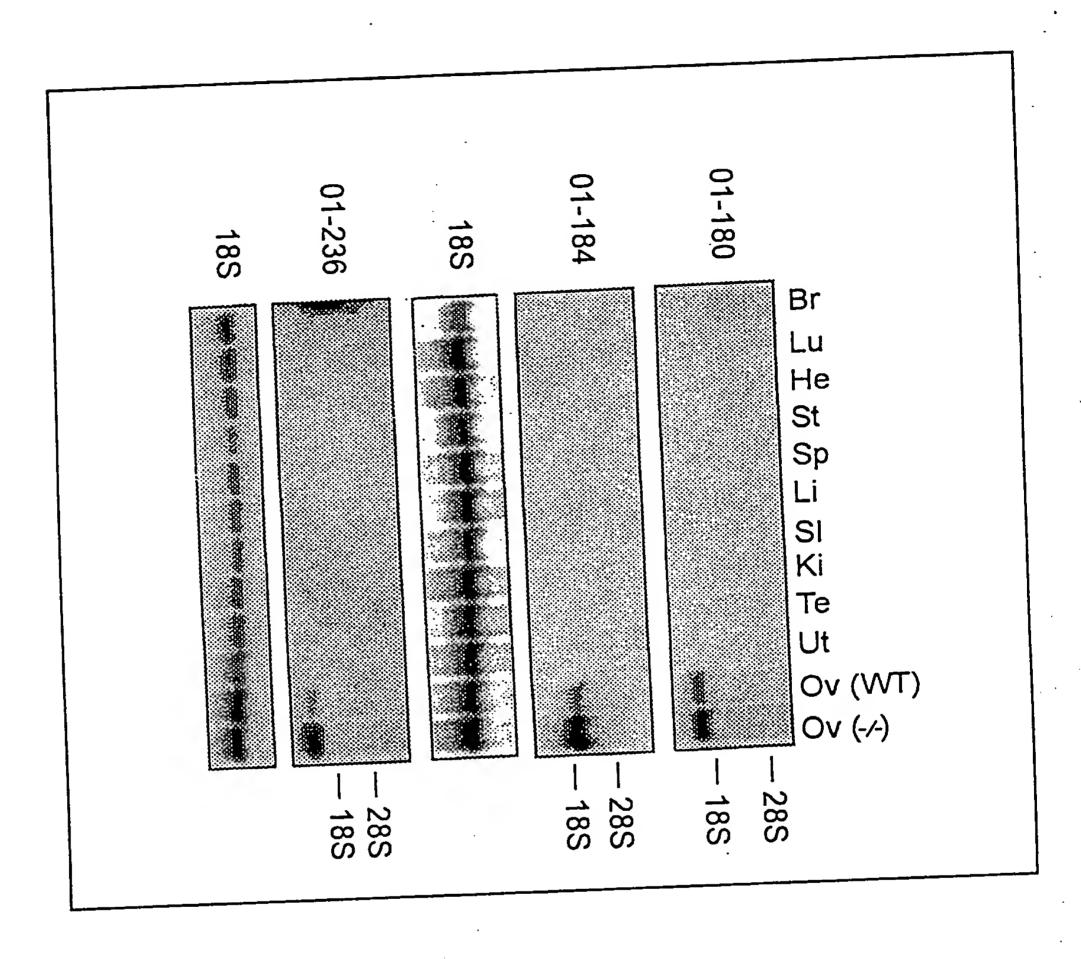


Figure 7

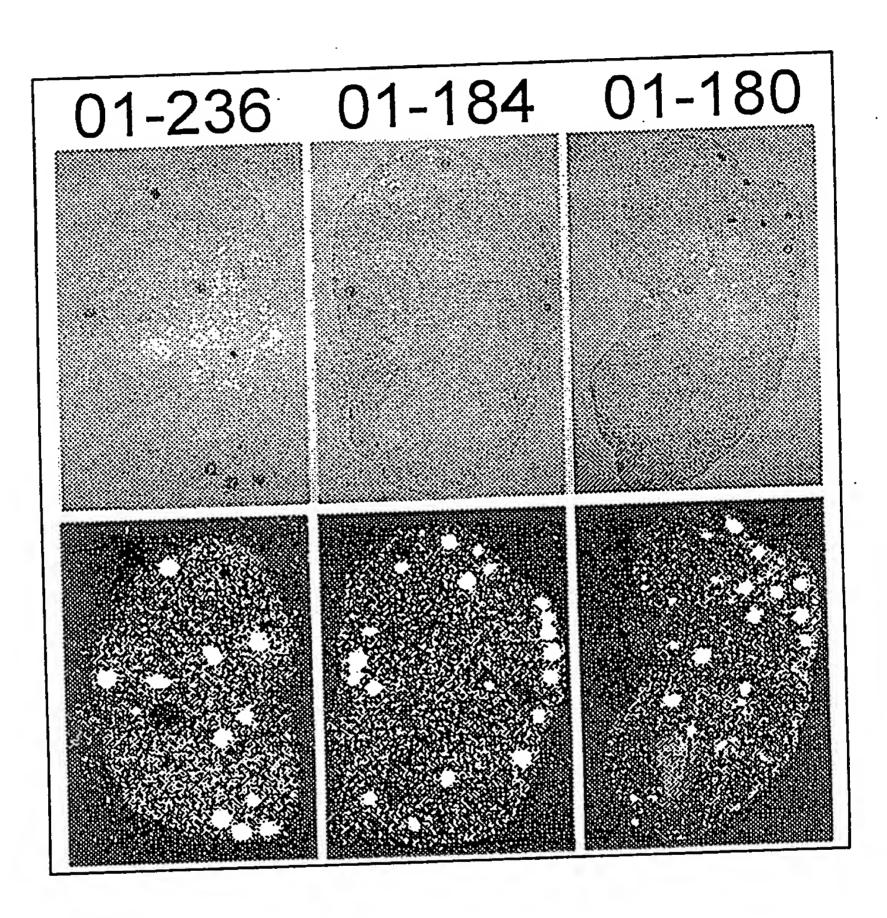


Figure 8

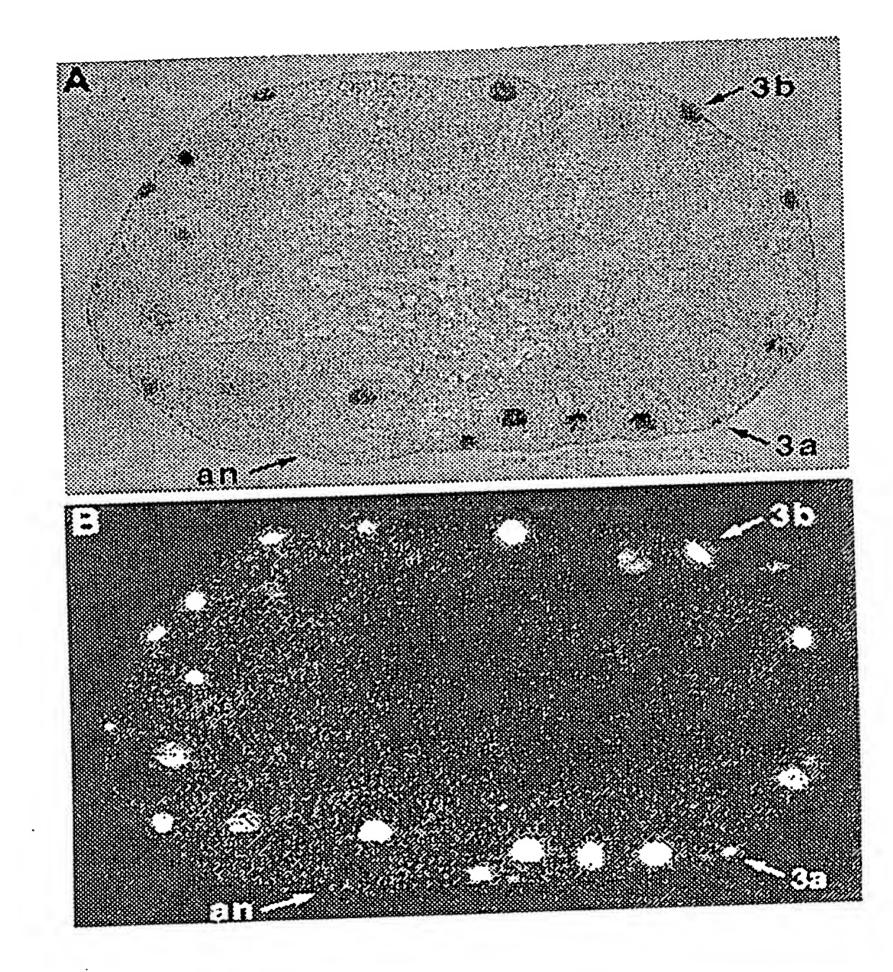


Figure 9

01-236 probe | NPM2 | 236-1 | 236-3 |

Figure 10

Npm2 Xnpm2	MSRHSTSSVTETTAKNMLWGSELN-QEKQTCTFRGQG-EKKDSCKLLL .
47 48	PKC STICLGEKAKEEVNRVEVLSQE-GRKPPITIATLKASVLPMVTVSGIELS RTVCLGDKAKDEFNIVEIVTQEEGAEKSVPIATLKPSILPMATMVGIELT
96 98	PKC PPVTFRLRTGSGPVFLSGLECYETSDLTWEDDEEEEEEEEEDEDEDADI
146 147	SLEEIPVKQVKRVAPQKQMSIAKKKKVEKEEDETVVRPSPQDKSPWKKEK QESPPKAVKRPAATKKAGQAKKKKLDKE-DESSEEDSPTKKGK
196 189	STPRAKKPVTKK 207

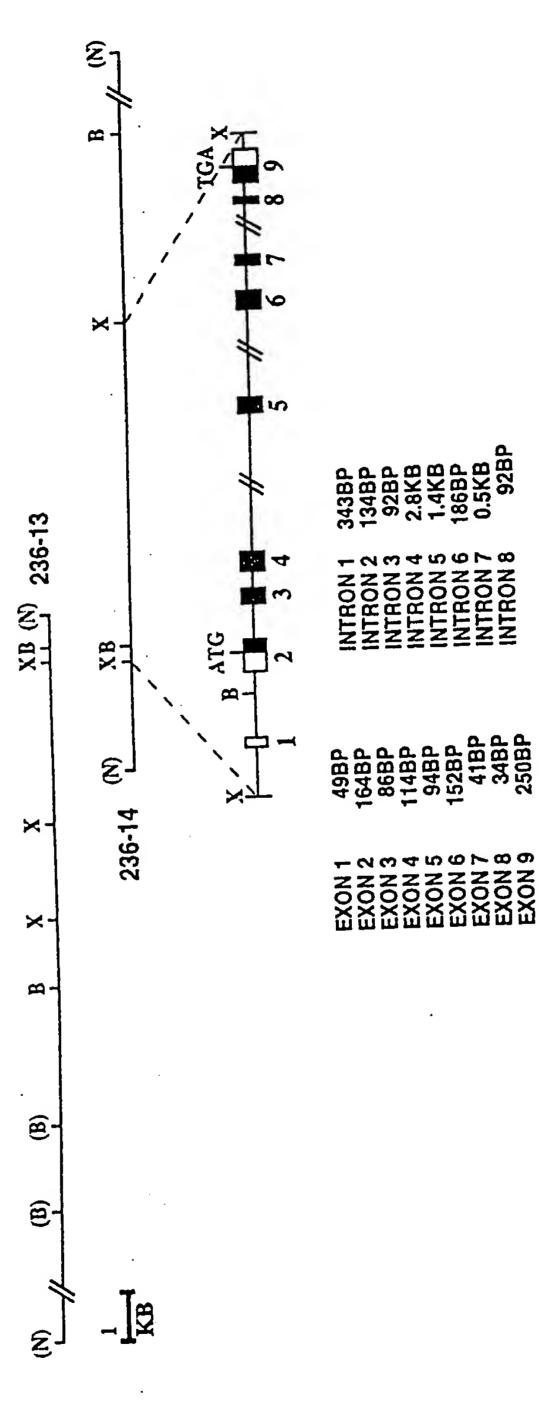


Figure 12

1

6

18

20

28

40

49

96

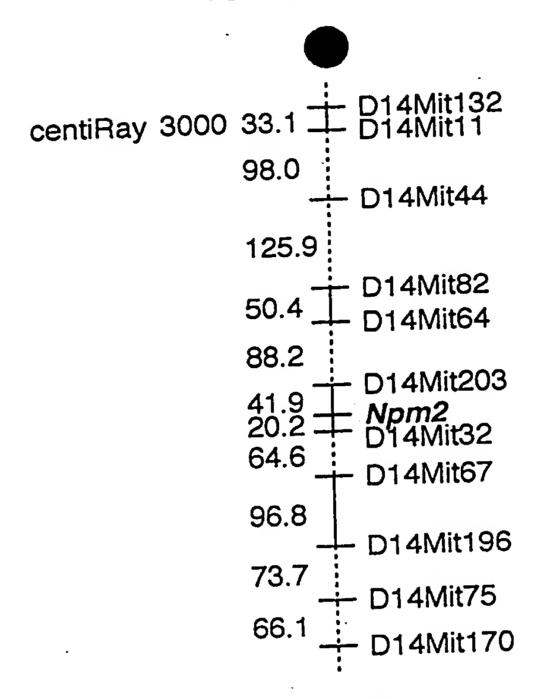
Mouse Npm2 Gene Sequences a cag cag agg tg at g ct cag a a at caa g tt tt a a cag agg g c cag g tgcttctagagtaggagggattgcacacctcccacccccctctttc ccaggcttcttaacagcctgctgtgggaagctgacccttagatggagc cctgaaGCCATATTGAGGACCTGCAGTAGAGGTGGAACCCATGACTGG CAGCGCAgtaagcttgagcagg... intron 1= 343bp ...ctttgcattactcagAACACAGTGATAACAGCTGAGCTCCAAGCA AGGACCCAGGACCTTGCCTCACCACAGACATAATCTTTCCCCACAACA ATG AGT CGC CAC AGC CCTCCACCAAGCCGCCCTGTAAATCGAC H R S M ACC AGC AGC GTG ACC GAA ACC ACA GCA AAA AAC ATG A K E V S CTC TGG Ggtaagggctaaggct... intron 2 = 134bp W L ...gtcttcgctgtgcagGT AGT GAA CTC AAT CAG GAA AAG CAG ACT TGC ACC TTT AGA GGC CAA TGC GAG AAG AAG E Q G R F С GAC AGC TGT AAA CTC TTG CTC AGC ACGgtgggtgtctccc T K C D aa... intron 3 = 92bp ...catcacctttctcagATC TGC CTG GGG GAG AAA GCC AAA GAG GAG GTG AAC CGT R N E K E K E 50 GTG GAA GTC CTC TCC CAG GAA GGC AGA AAA CCA CCA K R G E S Q L 62 ATC ACT ATT GCT ACG CTG AAG GCA TCA GTC CTG CCC I A T L K A S 74 ATGgtgagtcttctctcc... intron 4 = 2.8kb ...agaa M 86 gggggacacagGTC ACT GTG TCA GGT ATA GAG CTT TCT I E V T V S G 87 CCT CCA GTA ACT TTT CGG CTC AGG ACT GGC TCA GGA T F R L R T G

Figure 13A

CCT GTG TTC CTC AGT GGC CTG GAA TGT TAT Ggtaagtt E G S V F L 108 gtagccta... intron 5 = 1.35kb ...ggctacccattcc agAG ACT TCG GAC CTG ACC TGG GAA GAT GAC GAG GAA E D E D W D L T S T E 118 GAG GAG GAA GAG GAG GAA GAG GAT GAA GAT GAG D E E E E E E E E 130 GAT GCA GAT ATA TCG CTA GAG GAG ATA CCT GTC AAA E E A D I S L 142 CAA GTC AAA AGG GTG GCT CCC CAG AAG CAG ATG AGC K $\mathbf{A} \cdot \mathbf{P}$ Q Q V K R V 154 ATA GCA AAGgtggggggaaaagaa... intron 6 = 186bp A K I 166 ...tggtttttgttccagAAA AAG AAG GTG GAA AAA GAA E E K K V K K 169 GAG GAT GAA ACA GTA GTG AGgtaattcatgcagtt... V V T E D 176 intron 7 = 0.5kb ... ctattccctttccagG CCC AGC S P 183 CCT CAG GAC AAG AGT CCC TGG AAG AAG gtgagcaataag K K W P S K D 185 aag... intron 8 = 92bp ...ctcttatctgcacagGAG 194 AAA TCT ACA CCC AGA GCA AAG AAG CCA GTG ACC AAG K T P V A K K R K S P 195 AAA TGA CCTCATCTTAGCATCTTCTGCGTCCAAGGCAGGATGTCCA K 207 GCAGCTGTGTT<u>C</u>TGGTGCAGGTGTCCAGCCCCACCACCCTAGTCTGAA TGTAATAAGGTGGTGTGGCTGTAACCCTGTAACCCAGCCCTCCAGTTT CCGGAGGTTTTTGGTGAAGAGCCCCCAGCAAGTTCGCCTAGGGCCAC<u>A</u> <u>ATAAA</u>ATTTGCATGATCAGGacctccctctgcctccccctcggat gggtctcctcgctgctgcgatagctcatgtgcccagcagagggcaacc acgagcaagaaaccagccccatgt

Figure 13B

T31 RH Chr 14



Haplotypes for T31 Chr 14 near Npm2

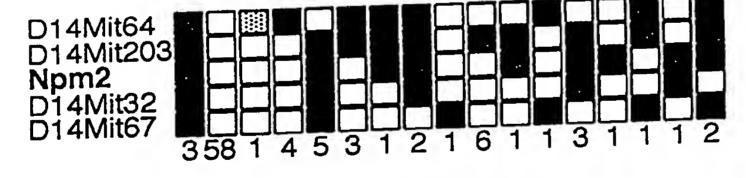


Figure 14

8 8 8	27 74 80 71 74	118 114 116	158 149	196 182	207
MNLSSASTEEKAVTTVLWGCELSQERRTWTFRPQLEGKQ MSRHSTSSVTETTAKNMLWGSELNQEKQTCTFRGQGEKKD MASTVSNTSKLEKPVSLIWGCELNEQDKTFEFKVE-DDEE	SC R L L L H T I C L G E K A K E E M H R V E I L P P A N Q E D K K M Q P V S C K L L L S T I C L G E K A K E E V N R V E V L S Q E G R K - P P I K C E H Q L A L R T V C L G D K A K D E F N I V E I V T Q E E G A E K S V P	TIASLOASVLPMVSMVGVQLSPVYT TIATLKASVLPMVTVSGIELSPVT -IATLKPSILPMATMVGIELTPPVT	FRC ERVE A S D L TWEEEEEEEEEEEEEEEEEEEEEEEEEDED AD I S L E E E C Y E T S D L TWEDDE EE E E E E E E E E D E D A D I S L E E - H V A M E E D Y S W A E E D E D E G E A E G E E E E E E E E E D D E S	SPVKQVKRLVPQKQASVAKKKLEKEEEIRASIPVKQVKRVBKBDETVVRPSIPVKQVKRVBKRKDEKEDETVVRPSIPPKAVKRRPARPATKKAGQAKKKLDKEDES	HNPM2 PVKKAKARAKRPGFKK MNpm2 PWKKEKSTPRAKRPVTKK XNpm2 PTKKGKGRKPAAKK
hinem2 xivom2	PANPWZ Mycm2 XNpm2	INFWZ Mom2 xNom2	MNPMZ MDMZ ZMDMZ	MNCm2 XNCm2	PANTANZ MNOm2 XNOm2

The state of the s

FIGURE 15

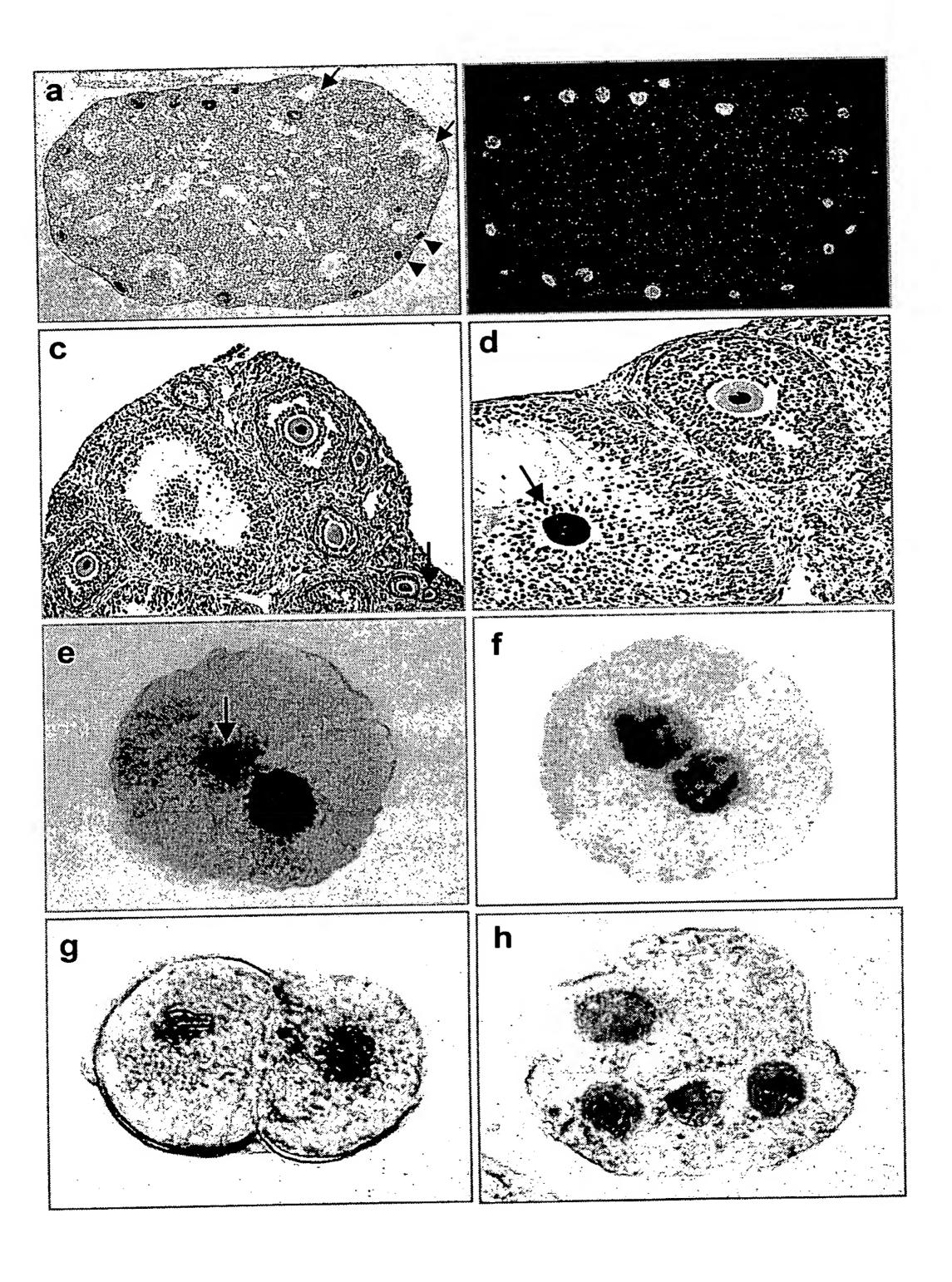


FIGURE 16

Hall the state of the state of

BgIII Digest 7.5 kb 10.3 kb 3' Probe BamH1 Digest 7.1 kb 10.7 kb 5' Probe

Recombinant

Wild-Type

3' Probe

5' Probe

1 장

FIGURE 17a

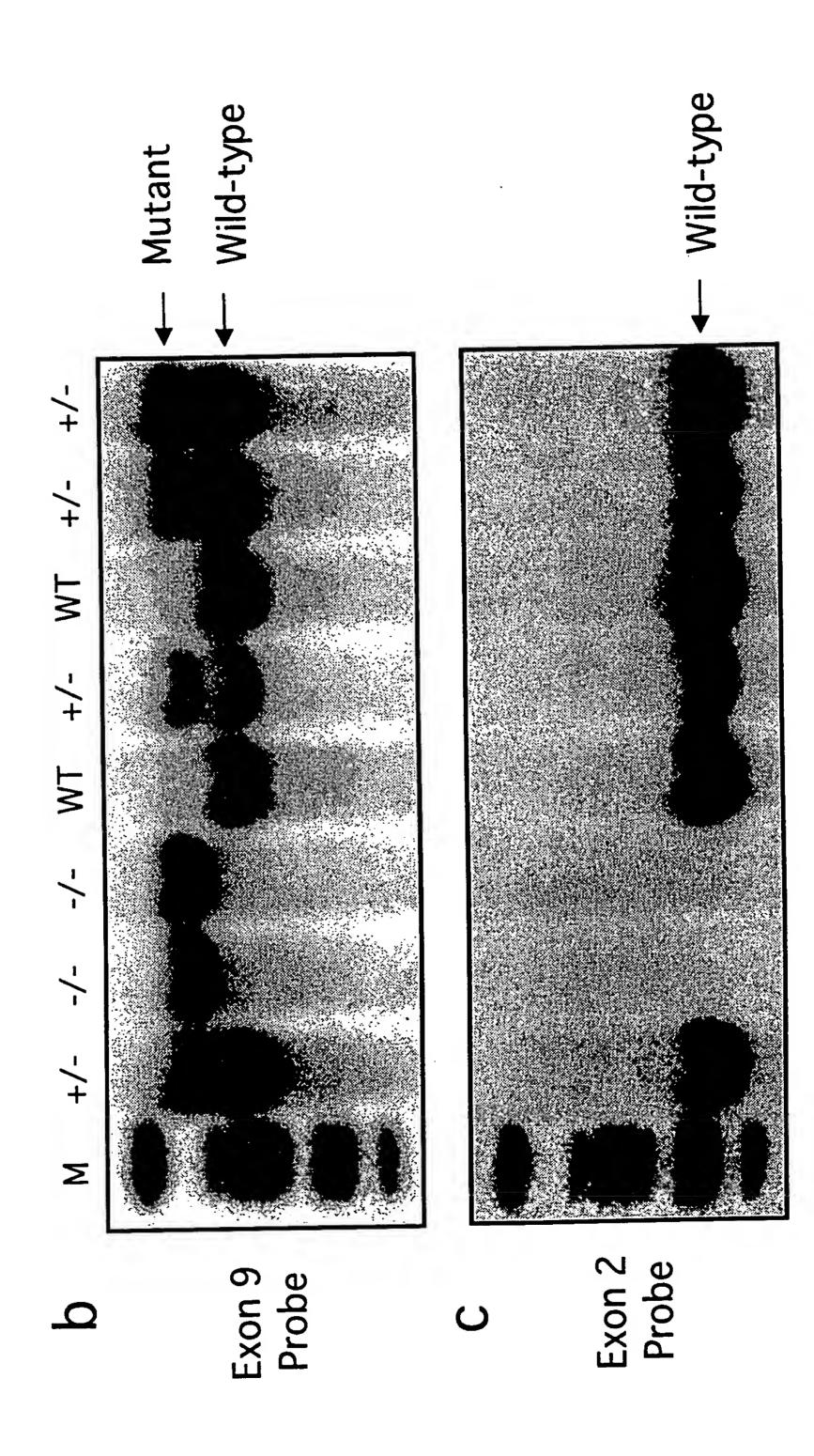


Figure 17b - Figure 17c

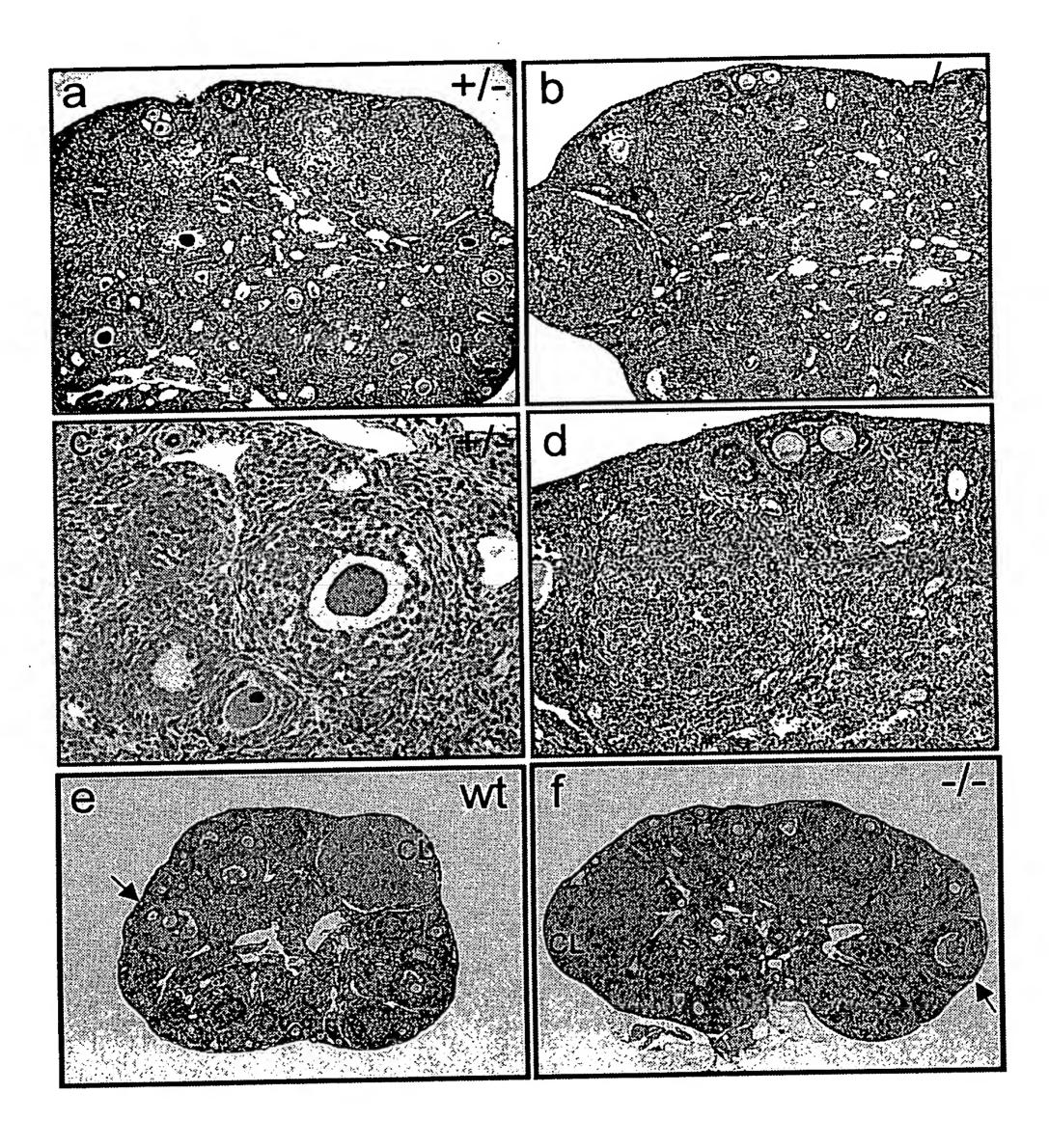


Figure 18

Figure 19a -

= t

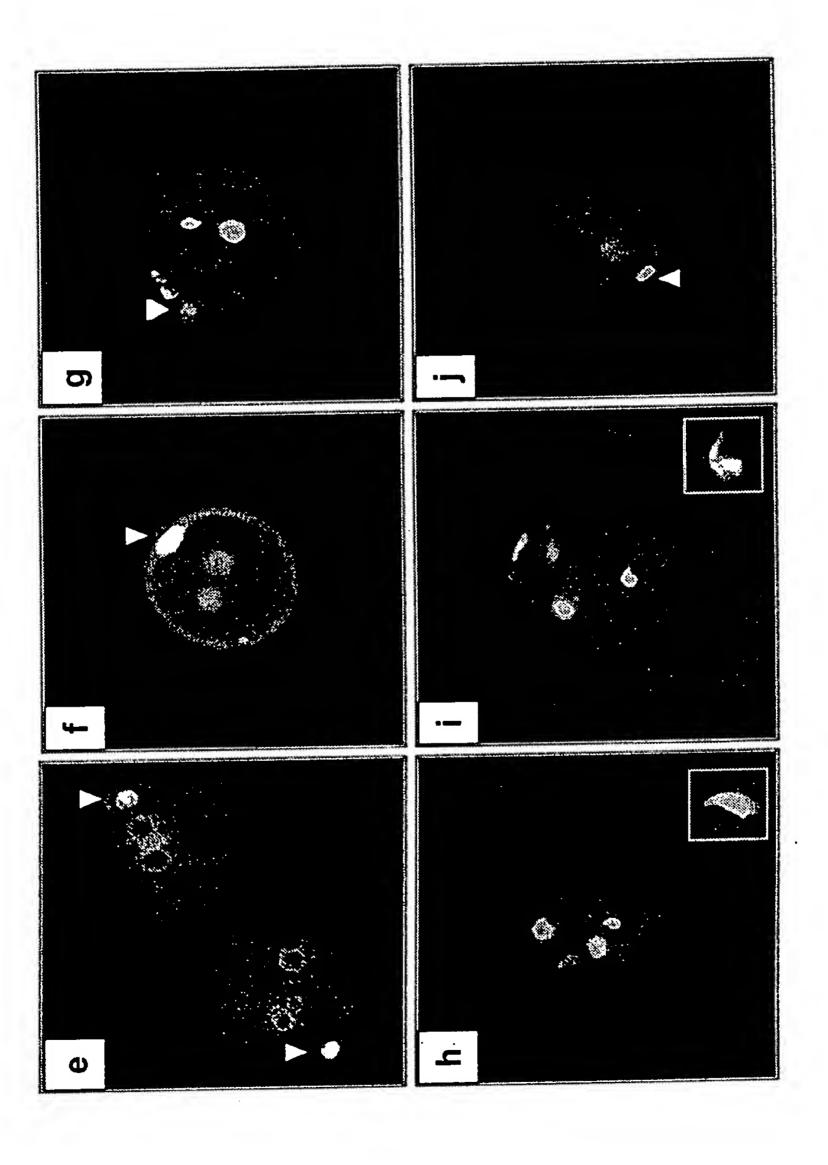


Figure 19e - 19

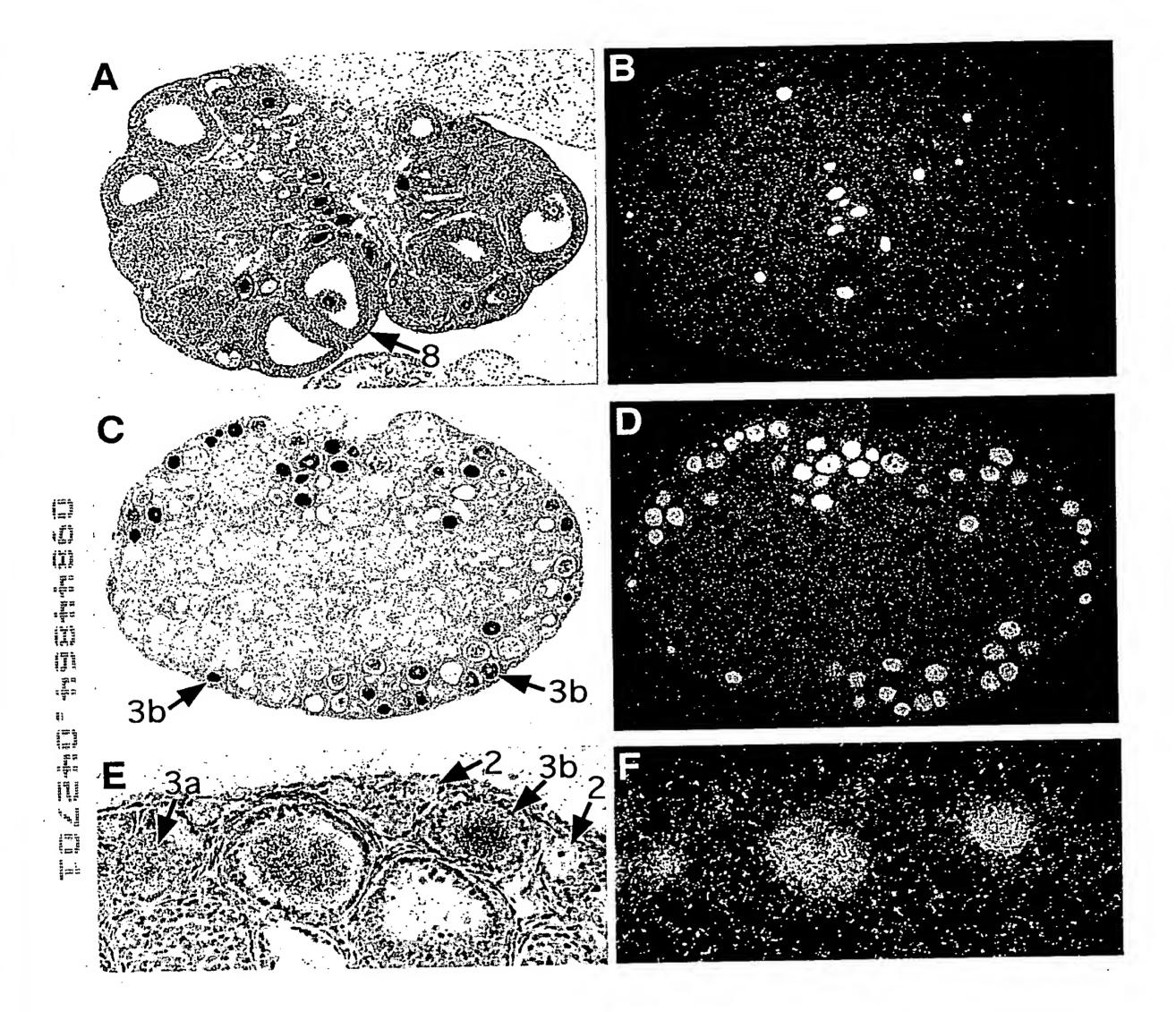
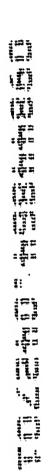
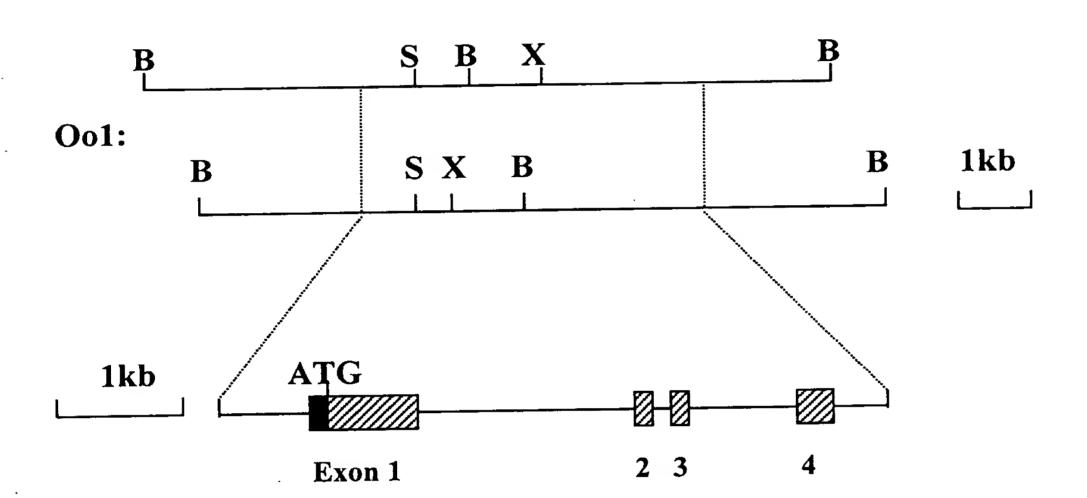
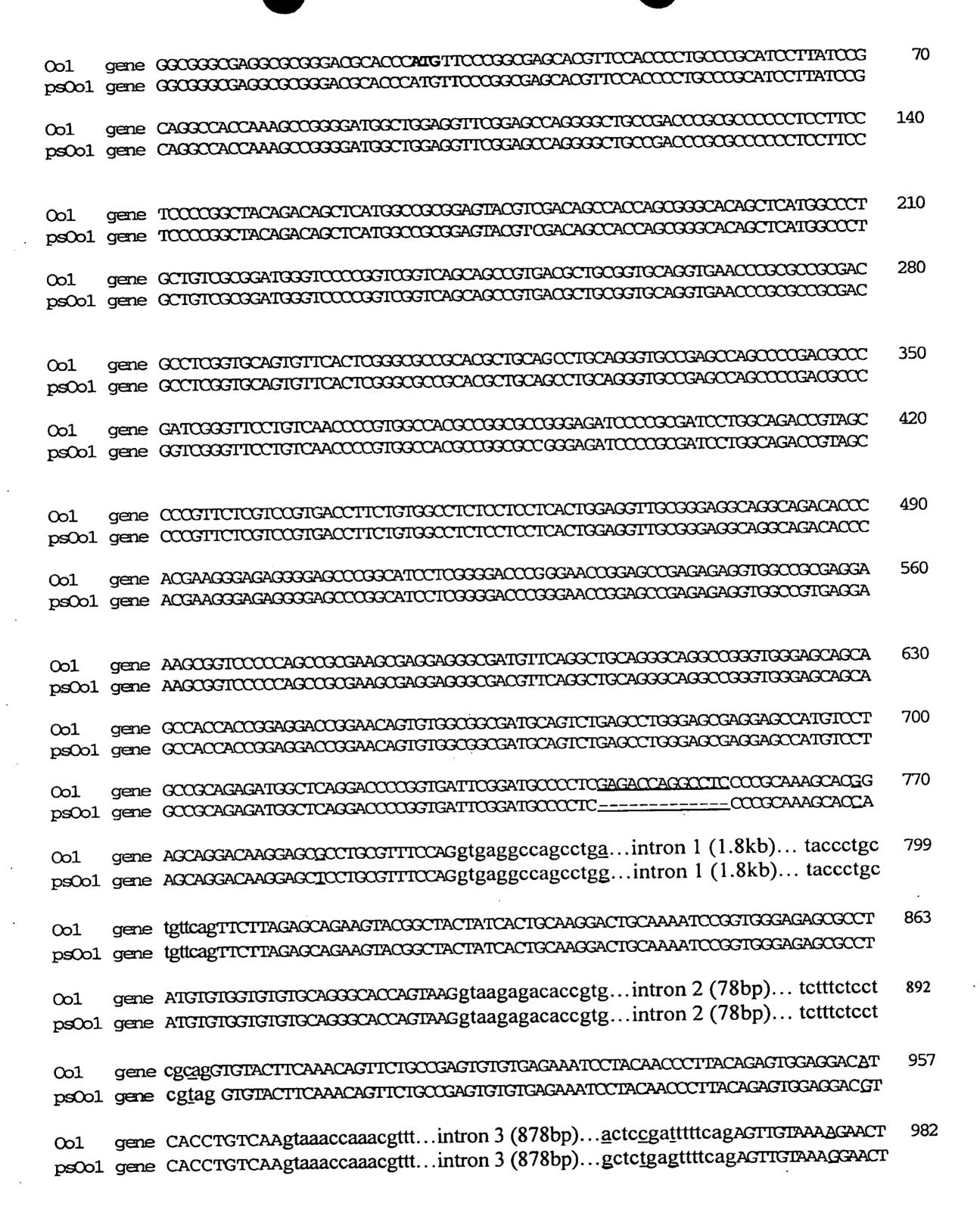


Figure 20

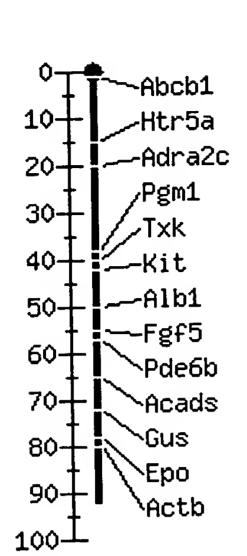


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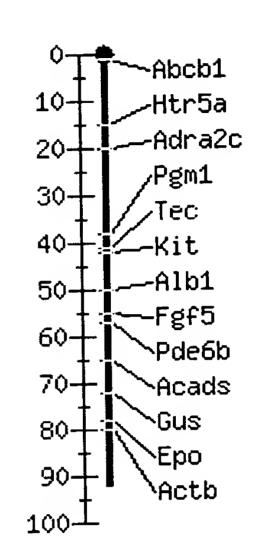




001	gene	AGATGIGCCIGCCCAGICAGACTICGCCACGIGGACCCIAA ACGCCCCCATCAGCAAGACTIGIGIGAGA AGATGIGCCIGCCCAGICAGACCTCGCCACGIGTACCTIAGACGCCCCCCATCAGCAAGACTIGIGIGAGA	1052
		THE PROPERTY OF THE PROPERTY O	1122
0-1	and a	CATGCAAGGACAAACGCTIGTCCTGCCTACCTACTACTACTACTACTACTACTACTACTACTACT	
		The second commence of	1192
001	gene	AACGITICIGCTAGATGGGGCTAATGGAATGGACAAGIGAGCTTICICCCCTCTTCACCTCTTCCCCTTTCCCACCTCTTCCCCTTTCCCCTTTCCCCTTTCCCCTTTCCCCTTTCCCC	
pscor		THE REPORT OF THE PROPERTY OF	1257
001 ps001	gene gene	CAAATICITCATGACAGACAGIGITACITGGATATAAAGCCIGIGAATAAAAGGTATIGCAAACA CAAATICITCATGACAGACAGIGITACITGGATATAAAGCCIGIGAATAAAAGGTATIGCAAACA	



 \mathbf{A}



B

Figure 23

BII MC1 tk BgIII BII **Bgl II Digest** 16.5 kb 9.0 kb Oo1 Gene Targeting Strategy 3'Probe 4 5.5kb 3' Probe MUT WT Homologous Recombination PGK hprt PGK hprt **Bgl II Digest** ATG 16.5 kb 8.8 kb BII BII 5'Probe 5' Probe MUT WT 1.5kb BgIII

BII

BII

Figure 24

29/29

Human NPM2 cDNA sequence: 924bp

CAGCCCGCTT CTCTGCCCGG AGCCATGAAT CTCAGTAGCG CCAGTAGCAC GGAGGAAAAG GCAGTGACGA CCGTGCTCTG GGGCTGCGAG CTCAGTCAGG AGAGGCGGAC TTGGACCTTC AGACCCCAGC TGGAGGGGAA GCAGAGCTGC AGGCTGTTGC TTCATACGAT TTGCTTGGGG GAGAAAGCCA AAGAGGAGAT GCATCGCGTG GAGATCCTGC CCCCAGCAAA CCAGGAGGAC AAGAAGATGC AGCCGGTCAC CATTGCCTCA CTCCAGGCCT CAGTCCTCCC CATGGTCTCC ATGGTAGGAG TGCAGCTTTC TCCCCCAGTT ACTTTCCAGC TCCGGGCTGG CTCAGGACCC GTGTTCCTCA GTGGCCAGGA ACGTTATGAA GCATCAGACC TAACCTGGGA GGAGGAGGAG GAAGAAGAAG GGGAGGAGGA GGAAGAGAA GAGGAAGATG ATGAGGATGA GGATGCAGAT ATATCTCTGG AGGAGCAAAG CCCTGTCAAA CAAGTCAAAA GGCTGGTGCC CCAGAAGCAG GCGAGCGTGG CTAAGAAAAA AAAGCTGGAA AAAGAAGAAG AGGAAATAAG AGCCAGCGTT AGAGACAAGA GCCCTGTGAA AAAGGCCAAA GCCACAGCCA GAGCCAAGAA GCCAGGATTC AAGAAATGAG GAGCCACGCC TTGGGGGGCA CGGTGCAAAG TGGGCCTTCC CTGGGCTGTG CTGCAGGCAC AGGGTGCCCC TGTCCAGCCC CTCCACCTGT GTCTGAATGC AACAGGGGTG TTGCGGGGGC AACATGAGAG CCCCTCACCC CCAACTCTCC ACTTTCAGGA GGCCCCCAGT GAAGAGCCCC ACCTCGGGGT CACAATAAAG TTGCCTGGTC AGGAAAAAA AAAAAAAAA AACGTTTGCG GCCGCAAGCT TATG

Human NPM2 Amino Acid sequence: 214aa

MNLSSASSTE EKAVTTVLWG CELSQERRTW TFRPQLEGKQ SCRLLLHTIC LGEKAKEEMH RVEILPPANQ EDKKMQPVTI ASLQASVLPM VSMVGVQLSP PVTFQLRAGS GPVFLSGQER YEASDLTWEE EEEEGEEEE EEEEDDEDED ADISLEEQSP VKQVKRLVPQ KQASVAKKKK LEKEEEIRA SVRDKSPVKK AKATARAKKP GFKK